PATENT
Case: OC01000KQ US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
RYBAK *ET AL.*	Examiner: A. HOLLERAN
For:	Group Art Unit: 1642
MELANOMA THERAPY	
Serial No.: 09/904,263	
Filed: July 12, 2001	

Schering-Plough Corporation
Kenilworth, New Jersey 07033-0530

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132 OF DAVID CUTLER, M.D., FRCPC.

I, Dr. David Cutler, declare and state as follows:

1. I earned an M.D. degree with honors from the University of Saskatchewan in 1982. I completed a rotating internship at North York General Hospital at the University of Toronto in 1983 and an Internal Medicine Residency at the Mayo Clinic in Rochester, Minnesota in 1986. From 1986 to 1988, I underwent Subspeciality Training in Endocrinology and Metabolism at the University of Toronto. I was a Research Fellow at the UCSD Medical Center in San Diego, California from 1988 to 1991. Attached is a copy of my *curriculum vitae* (Exhibit A).

2. Since 1996, I have been employed at Schering-Plough Corporation, the assignee of the present patent application. I am currently Senior Director, Early Clinical Research and Experimental Medicine. At Schering-Plough, I have

supervised clinical trials using Intron (an interferon alpha 2b) and PEG-INTRON (a pegylated interferon alpha 2b).

3. I am familiar with the January 29, 2003, May 20, 2003, and June 29, 2004 Office Actions issued in the above-identified application and with the arguments that have been made by Applicants in the Responses filed February 26, 2003, October 20, 2003 and March 22, 2004 in support of patentability of the pending claims.

I have reviewed the Declaration of Dr. Craig Tendler, which was filed in this application on October 20, 2003, and agree with the points made therein. I understand the Tendler Declaration opined that because pegylation of a given molecule changes both the molecular and pharmacokinetic properties of the molecule, the pegylated and unpegylated versions of the molecules should be considered to be two different drugs (Tendler Declaration ¶ 5). Therefore, using unpegylated interferon alpha to treat melanoma is not predictive of using pegylated interferon alpha to safely and efficaciously treat the disease (Tendler Declaration ¶4). Specifically, Dr. Tendler stated that the relationship of peak plasma levels (Cmax) to total drug exposure (AUC) is different for pegylated interferon alpha compared to that of unpegylated interferon alpha, and that administration of pegylated interferon alpha results in a decreased Cmax and an increased AUC as compared to native interferon (Tendler Declaration ¶6).

4. I am aware that in the Office Action dated June 29, 2004, the Examiner questions whether a decrease in peak plasma levels due to pegylation of interferon alpha is true for all forms of pegylated interferon alpha (Office Action p. 3).

5. I make this Declaration to supplement the submission of data that supports the conclusion that <u>at the doses defined by the pending claims to treat melanoma</u>, administration of <u>PEG_{12000}</u> interferon alpha resulted in lower peak plasma levels of interferon alpha activity but prolonged total drug exposure as compared to administration of unconjugated interferon alpha.

6. Table 1, below, contains pharmacokinetic data indicating that at the doses used to treat melanoma in humans (25 MIU for Interferon alpha and 3 µg/kg for PEG_{12000}-interferon alpha), the C_{max} is significantly lower when the pegylated version of interferon alpha was administered than when the unconjugated version was administered. Data presented below are plasma concentrations of bioactive interferon measured in a bioassay and reported as international units (IU/mL). These data are extracted from a multiple dose safety and tolerability study of several dose levels of PEG Intron and Intron A. Post hoc determination of the Cmax and AUC are presented. The data from the highest dose of PEG Intron, 2 µg/kg are normalized to a clinical dose of 3 µg/kg. Similarly, the date from the Intron A treatments at 3 MIU are normalized to a clinical dose of 25 MIU.

Table 1.

Individual and Mean Cmax

PEG 2 µg/kg Wk 4	Intron 3 MIU Wk 4
300	38
150	28
94	38
113	19
150	19
225	14
	47
	56
	23
	38
	94
	300
	75
	75
	56
	38
Mean	**Mean**
172	**59.875**
Normalized Mean	**Normalized Mean**
258	**479**

7. Table 2, below, contains data generated in the same study. This table shows that the total drug exposure (AUC) was higher in patients in which PEG_{12000} interferon alpha was administered compared to those in which comparable doses of native interferon alpha was administered. Data are again normalized to the clinical doses of 3 µg/kg for PEG Intron and to 25 MIU for Intron A. Data for PEG Intron are calculated to 7 days, while data for Intron are truncated at 48 hours.

Table 2

Individual and Mean AUC

PEG 2 µg/kg Wk 4	Intron 3 MIU Wk 4
1578	907
2230	541
8703	1110
8006	353
9538	437
24468	242
	1584
	1295
	711
	806
	1594
	3685
	2452
	1642
	2767
	1420
Mean	**Mean**
13116	**1347**
Normalized Mean	**Normalized Mean**
19673	**11217**

8. Therefore, I am of the opinion that at the doses used to treat melanoma, administration of PEG_{12000} interferon alpha resulted in lower peak plasma levels of interferon alpha activity but prolonged total drug exposure as compared to administration of unconjugated interferon alpha.

9. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application and any patent issued thereon.

Dec 22, 2004.
Date

David Cutler, M.D., FRCP(C)

Latest revision: 8/11/04

CURRICULUM VITAE

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EDUCATION:

1988 - 1991	Research Fellow UCSD Medical Center San Diego, CA Supervisor: Dr. O. Kolterman
1986 - 1988	Subspeciality Training in Endocrinology and Metabolism University of Toronto Toronto, Ontario
1983 - 1986	Internal Medicine Residency Mayo Clinic Rochester, MN
1982 - 1983	Rotating Internship North York General Hospital University of Toronto Toronto, Ontario
1982	University of Saskatchewan M.D., Magna Cum Laude
1976	University of Saskatchewan Major: Microbiology
1975	University of Regina

LANGUAGES: English

HONORS AND AWARDS :

1979	Graduate scholarship for academic excellence
1978	Graduate scholarship for academic excellence
1977	Graduate scholarship for academic excellence
1976	Undergraduate scholarship for academic excellence
1975	Undergraduate scholarship for academic excellence

CURRENT LICENSURE/CERTIFICATION:

1991-Present	State of New Jersey - MA 57335
1987-Present	State of California - G062988
1983-1987	State of Minnesota
1982-Present	Ontario College of Physicians and Surgeons - 50315
1989	Diplomate American Board of Endocrinology and Metabolism
1988	Fellow of the Royal College of Physicians and Surgeons of Canada F.R.C.P.(C)
1986	Diplomate American Board of Internal Medicine
1985	Diplomate National Board of Medical Examiners
1983	Licentiate Medical Council of Canada (L.M.C.C.)

ACADEMIC/HOSPITAL APPOINTMENTS: None

COMMITTEES/SOCIETIES/PROFESSIONAL AFFILIATIONS::

Fellow	Royal College of Physicians and Surgeons of Canada
Member	American College of Physicians
Member	American Diabetes Association
Member	American Society for Clinical Pharmacology and Therapeutics
1998-2002	Reviewer - Annals of Pharmacotherapy
1997-2002	Member - Robert Wood Johnson Medical Center - Clinical Research Center Advisory Board
3/88-6/88	Chief endocrine resident St. Michael's Hospital, Toronto, Ontario, Canada
7/87-12/87	Chief endocrine resident Wellesley Hospital, Toronto, Ontario, Canada
1/87-6/87	Chief endocrine resident Toronto General Hospital, Toronto, Ontario, Canada
7/86-12/86	Chief endocrine resident Mount Sinai Hospital, Toronto, Ontario, Canada

WORK EXPERIENCE:

2002-Present	Senior Director Early Clinical Research and Experimental Medicine Schering-Plough Research Institute
2001-2002	Senior Director Clinical Pharmacology Schering-Plough Research Institute
1998 - 2001	Director Clinical Pharmacology Schering-Plough Research Institute
1996 - 1998	Senior Clinical Research Physician Clinical Pharmacology Schering-Plough Research Institute

1994 - 1996	Senior Associate Director Clinical Pharmacology Schering-Plough Research Institute
1991 - 1994	Associate Director Clinical Pharmacology Schering-Plough Research Institute

PATENTS

5,908,621 - Polyethylene glycol modified interferon therapy
5,945,097 - Method for lowering cholesterol levels with Interleukin-10
6,096,757 - Method for treating proliferative diseases
6,117,074 - Polyethylene glycol modified interferon therapy
6,333,333 - Method for treating proliferative diseases
6,461,605 - B1- Continuous low-dose cytokine infusion therapy
6,524,570 – B1- Polyethylene Glycol Modified Interferon Therapy

PUBLICATIONS/PRESENTATIONS:

Presentations:

1. Freidenberg, G., Jones, M., Hall, B., **Cutler, D.**, Kaufmann, S.: A new syndrome of insulin resistance diabetes mellitus and mandibuloacral dysplasia. Western Society of Pediatric Research, Carmel, CA, 1989.

2. **Cutler, D.L.**, Park, S.W., Hanchett, C., Hickman, M., Bell, J., Gray, G., Kolterman, O.: Low carbohydrate diet does not cause insulin resistance in exercise-trained subjects. American Diabetes Association Annual Meeting, Atlanta, Georgia, 1990.

3. Park, S., **Cutler, D.**, Crone, L., Bell, J., Verity, L., Kolterman, O.: Insulin and exercise interact synergistically to activate glycogen synthase. American Diabetes Association Annual Meeting, Atlanta, Georgia, 1990.

4. **Cutler, D.L.**, Kolterman, O.G., Hintz, R.L., Prince, M.J. Tumor associated hypoglycemia: IGF-I and II prohormone associated augmentation of glucose oxidation. Western Section AFCR, Carmel, CA, 1991.

5. Pajkrt, D., **Cutler, D.**, Grint, P., Tiel, M., van Deventer, S.J.H. Recombinant human IL-10 (rhuIL-10) reduces cytokine release and granulocyte recruitment in lungs in human endotoxemia. 36th Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC), September 15-18, 1996, New Orleans, Louisiana, (Abstract G32): 149, 1996.

6. Haehner-Daniels, B.D., **Cutler, D.L.**, Affrime, M.B., Gorski, J.C., Hall, S.D. The selective in vivo increase of cytochrome P450 2C8/9 activity by interleukin-10 (IL-10). 99th American Society for Clinical Pharmacology and Therapeutics, March 30 - April 1, 1998, New Orleans, Louisiana.

7. Radwanski, E., Chakraborty, A., VanWart, S., **Cutler, D.L.**, Affrime, M.B., Jusko, W.J. Pharmacokinetics and dynamics (cytokine suppression) of IV and SC recombinant human interleukin-10. 99th American Society for Clinical Pharmacology and Therapeutics, March 30 - April 1, 1998, New Orleans, Louisiana.

ABSTRACTS

1. Freidenberg, G., Jones, M., Hall, B., **Cutler, D.**, Kaufmann, S.: A new syndrome of insulin resistance diabetes mellitus and mandibuloacral dysplasia. Clinical Research, 37(1), p192A, 1989.

2. **Cutler, D.L.**, Park, S.W., Hanchett, C., Hickman, M., Bell, J., Gray, G., Kolterman, O.: Low carbohydrate diet does not cause insulin resistance in exercise-trained subjects. Diabetes, 39;Supp. (1), p.64A, 1990.

3. Park, D., **Cutler, D.**, Crone, L., Bell, J., Verity, L., Kolterman, O.: Insulin and exercise interact synergistically to activate glycogen synthase. Diabetes, 39;Supp.(1), p13A, 1990.

4. **Cutler, D.L.**, Kolterman, O.G., Hintz, R.L., Prince, M.J. Tumor associated hypoglycemia: IGF-I and II prohormone associated augmentation of glucose oxidation. Clinical Research 39;1, 101A, 1991.

5. Freidenberg, G., **Cutler, D.**: Insulin resistance, diabetes mellitus and mandibuloacral dysplasia. Proc 71st Endocrine Society Abstract 150.

6. Prince, M.J., Kolterman, O.G., **Cutler, D.L.**: Predominant augmentation of glucose oxidation in tumor associated hypoglycemia. Diabetes 40;(Supp 1):100A, 1991.

7. **Cutler, D.L.**, Kolterman, O.G.: Vanadate increases pyruvate dehydrogenase activity in diabetic rats. Diabetes 40;(Supp 1):261(A), 1991.

8. Freidenberg, G., Kushari, J., **Cutler, D.**: A case of diabetes mellitus and insulin resistance: result of defects in the insulin receptor. Diabetes 40;(Supp 1):113A, 1991.

9. Crone, L.L., Verity, L.S., **Cutler, D.L.**, Kolterman, O.G., Nichols, F.N.: (Effect of) acute exercise on glucose disposal in well and poorly controlled Type I diabetics v normals. Medicine and Science in Sports and Exercise 23;4 (Supp):S100, 1991.

10. **Cutler, D.L.**, Park, S.W., Hanchett, K., Hickman, M., Bell, J.M., Gray, C., Kolterman, O.G.: Interactions between exercise training and carbohydrate restriction. Clinical Research 38;1, 118A, 1990.

11. Macherone, A., Batra, V., Lin, C., Korduba, C., Affrime, M., Teal, M., **Cutler, D.**, Radwanski, E.: Comparison of the pharmacokinetics of isepamicin in young and geriatric volunteers. Pharmaceutical Research 10;10:Suppl, 317, 1993.

12. Radwanski, E, Nomeir, A, **Cutler, D.**, Fettner, S., Lin, C., Affrime, M., Batra, V. Pharmacokinetics of ceftibuten administered with and without Mylanta II or ranitidine. Pharmaceutical Research 10;10:Suppl, 310, 1993.

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14. Radwanski, E., Macherone, A., **Cutler, D.**, Huhn, R., Affrime, M., Jacobs, S., Cayen, M.N., Batra, V.K.: Rising single-dose safety and tolerance of IL-10 in normal male volunteers. Pharmaceutical Research 11;10:Suppl, 339, 1994.

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21. **Cutler, D.L.**, Kosoglou, T., Sabo, R., Affrime, M., Katz, A., Ginsberg, H.: Effect of SCH 48461 on oral cholesterol absorption. Clinical Pharmacology and Therapeutics 59;2:194, 1996.

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31. Bunnell, E., Habet, K., **Cutler, D.**, Orencole, S., Affrime, M.B., Dinarello, C., Parrillo, J.E. Inhibition of Pro-Inflammatory Cytokines by Interleukin-10 in Human Experimental Endotoxemia. American Thoracic Society 1997 Meeting.

32. **Cutler, D.L.**, Affrime, M.B., Herron, J., Sabo, R. Recombinant Human IL-10 (rHuIL-10) Inhibits Delayed Type Hypersensitivity Response (DTH) in Healthy Volunteers. Clinical Pharmacology and Therapeutics 61; 2:160, 1997.

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34. Radwanski, E., Chakraborty, A., VanWart, S., **Cutler, D.L.**, Affrime, M.B., Jusko, W.J. Pharmacokinetics and Dynamics (Cytokine Suppression) of IV and SC Recombinant Human Interleukin-10. Clinical Pharmacology and Therapeutics 63; 2:240, 1998.

35. Gorski, J.C., Haehner, B.D., **Cutler, D.**, Affrime, M.B., Hall, S.D. Lack of Correlation Between Intravenous Midazolam and Oral Dextromethorphan CYP3A Phenotypes. Clinical Pharmacology and Therapeutics 63; 2:150, 1998.

36. Haehner-Daniels, B.D., **Cutler, D.L.**, Affrime, M.B., Gorski, J.C., Hall, S.D. The Selective In Vivo Induction of Cytochrome P450 2C8/9 by Interleukin-10 (IL-10). Clinical Pharmacology and Therapeutics 63; 2:241, 1998.

37. Chakraborty, A., Blum RA., Mis, SM, **Cutler, D.L.**, Jusko, WJ. Pharmacokinetic – Pharmacodynamic Interaction IL-10 and Prednisone in Normal Volunteers. AAPS Pharm Sci 1(1) Suppl. (Abstract 3806), 1998.

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43. Awada, A., Eskens F., Piccart, MJ., Van der Gaast, A., Bleiberg, H., **Cutler, D.L.**, Fumoleau, P., Wanders, J., Faber, MN., Verweij, J., A Clinical, Pharmacodynamic and Pharmacokinetic Phase I Study of SCH 66336 (SCH) an Oral Inhibitor of the Enzyme Farnesyl Transferase given once Daily in Patients with Solid Tumors. Proceedings AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Theropeutics. 5, 1999.

44. Denis, L., Tolcher, A., Figueroa, J., Drengler, R., Geyer, C., Eckhardt, SG., **Cutler, D.**, Reyderman, L., Von Hoff, D., and Rowinsky, E. Protracted Daily Administration of Temozolomide is Feasible; A Phase I and Pharmacokinetic/Pharmacodynamic Study. Proceedings of ASCO 19:202,2000.

45. Figueroa, J., Tolcher, A., Denis, LJ., Drengler, R., Geyer, C., Eckhardt, SG., **Cutler, D.**, Reyderman, L., Von Hoff, D., and Rowinsky, E. Protracted Cyclic Administration of Temozolomide is Feasible; A Phase I, Pharmacokinetic and Pharmacodynamic Study. Proceedings of ASCO 19:222, 2000.

46. Tolcher, A., Felton, S., Gerson, S.L., Edwards, T., Patnaik, A., Smith, L., Geyer, C., Johnson, T., Reyderman, L., **Cutler, D.**, Rowinsky, E. Persistent and Marked Inactivation

of O^6-Alkylguanine-DNA Alkytransferase Activity (AGAT), A Mechanism of Resistance to Alkylators, with Protracted Low-Dose Oral Schedules of Temozolamide. Proceedings of ASCO 19:175,2000.

47. Hurwitz, H., Amado, R., Prager. D., Hecht, J., Cohen, D., Conway, D., Kadib, L., Mayers, A., Calzetta, A., Statkevich, P., **Cutler, D.**, and Rosen, L. Phase I Pharmacokinetic Trial of the Farnesyl Transferase Inhibitor Sch 66336 Plus Gemcitabine in Advanced Cancers. Proceedings of ASCO 19:185,2002.

48. Kosoglou, T., Meyer, I., **Cutler, D.**, Musiol, B., Yang, B., Zhu, Y., Maxwell, S., Affrime, M., Veltri, E. Pharmacodynamic Interaction Between the Selective Cholesterol Absorption Inhibitor Ezetimibe and Lovastatin. International Congress on Coronary Artery Disease, Abstract book 3:101 (Abstract 390), 2000

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INVITED LECTURES

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2. International Symposium on Treatments in Hepatology March 15-17, 1995; Barcelona, Spain. Pharmacology of Interferon.

3. American Society for Clinical Pharmacology and Therapeutics Rheumatology, Immunology and Inflammation Section Meeting March 6, 1997; San Diego, California. Pharmacology of rHuIL-10.

4. 4th International Congress on The Immune Consequences of Trauma, Shock and Sepsis, March 4, 1997; Munich, Germany. Multiple-Dose Pharmacology of rHuIL-10.